AUGUST 20, 1984
CHEMICAL ENGINEERING

NEWS

Chemical company earnings continue surge in second quarter
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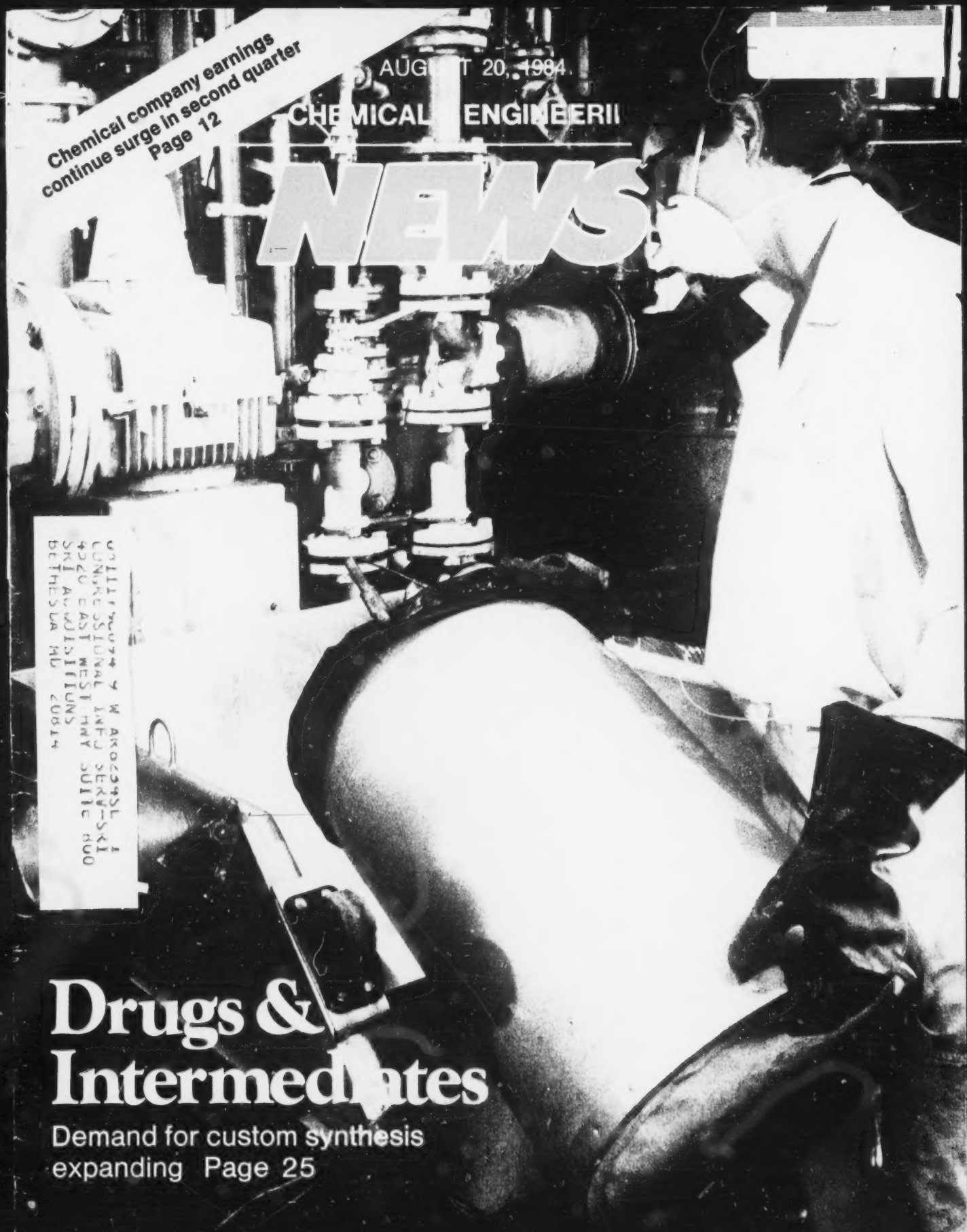

Drugs & Intermediates

Demand for custom synthesis expanding Page 25

CHEMICAL & ENGINEERING NEWS

Volume 62, Number 34
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AUGUST 20, 1984

News of the Week

■ **New study of babies whose fathers were Vietnam veterans shows no evidence of higher than normal rate of birth defects.** **Page 6**

■ **Jet fuel additive claimed to prevent postcrash fires to undergo critical test.** **Page 7**

■ **Scientists offer to go to the U.S.S.R. as guarantors if Soviets allow Elena Bonner to seek medical treatment abroad.** **Page 7**

■ **SEC and Stauffer Chemical resolve suit over firm's accounting practices.** **Page 8**

■ **Three companies lease plots in dioxin-contaminated Times Beach, Mo., for research purposes.** **Page 8**

Cover: Workman charges a reactor at Eastman Kodak's custom synthesis pilot plant in Rochester, N.Y.

Business

The healthy gains in U.S. chemical industry earnings continued in the second quarter, through stepped-up demand for products, stable costs, and increased productivity. **Page 12**

International Business

Combined earnings of Canada's four largest chemical firms rose to $37.2 million in the second quarter, 65% ahead of first-quarter 1984, but not all firms performed equally. **Page 18**

Government

House-passed bill to extend Superfund would raise taxes, require EPA to follow a mandatory cleanup schedule. **Page 20**

California officials and scientists move to correct mistakes that turned Stringfellow waste dump problem into emergency. **Page 22**

Technology

CHEMRAWN III, on resource material conversion, emphasized the need to develop and implement new technologies for making chemicals when oil supplies eventually are depleted. **Page 63**

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Product Report

Custom synthesis of drugs and intermediates is a thriving, if sometimes risky, business. **Page 25**

Chemical Firms Post Strong Gains in Second Quarter

William J. Storck, C&EN New York

As indicated by early company reports, earnings of U.S. chemical producers continued to grow strongly in the second quarter, climbing an average of 52% from those in second-quarter 1983. Coupled with the even stronger 70% annual growth in this year's first quarter, the industry's earnings for first-half 1984 gained 59% from last year's first half.

This happy state of affairs has been spurred by a combination of increased demand for products, relatively stable costs, and increased efficiencies. Although the earnings gains extended widely among U.S. chemical companies as well as diversified and oil companies that produce chemicals, the gains were larger for basic chemical companies than for the smaller, more specialty-oriented firms. And they were bigger for chemical and diversified firms than for oil companies.

Based on results posted by 30 of the largest U.S. chemical companies for the second quarter, the 52% increase brought combined earnings of these companies to $1.13 billion. Combined sales of these companies rose 11% from last year's second quarter to $18.6 billion. The much larger increase in earnings than in sales gave a healthy push to chemical profitability in the quarter: Average profit margin rose to 6.2% from 4.5% a year earlier.

Greater demand in many of chemicals' end-use markets played no small part in the industry's achieving these results. For instance, the automobile market has continued strongly, and housing and commer-

Chemical industry leaders for the second quarter . . .

Sales

Rank		$ Millions	Rank 1983
1	Dow Chemical	$2986.0	1
2	Union Carbide	2403.0	2
3	Monsanto	1801.0	3
4	W. R. Grace	1741.4	4
5	PPG Industries	1100.0	5
6	American Cyanamid	1000.0	6
7	Celanese	860.0	7
8	Hercules	662.0	8
9	Rohm & Haas	554.8	9
10	Olin	545.3	10

Earnings[a]

	$ Millions	Rank 1983
Dow Chemical	$184.6	2
Monsanto	145.0	1
Union Carbide	126.0	4
PPG Industries	86.1	3
American Cyanamid	57.4	6
W. R. Grace	57.4	7
Hercules	53.4	8
Rohm & Haas	51.9	5
Celanese	47.0	12
Air Products	38.2	10

Profitability

	Earnings as % of sales	Rank 1983
International Flavors	16.2%	1
Loctite	11.9	4
Freeport-McMoRan	11.9	2
Nalco Chemical	11.1	3
First Mississippi	9.8	9
Lubrizol	9.7	5
Rohm & Haas	9.4	6
Petrolite	8.5	7
Air Products	8.5	13
Hercules	8.1	11
Monsanto	8.1	12

. . . and for the first six months of 1984

Sales

Rank		$ Millions	Rank 1983
1	Dow Chemical	$5902.0	1
2	Union Carbide	4796.0	2
3	Monsanto	3533.0	3
4	W. R. Grace	3238.7	4
5	PPG Industries	2100.0	5
6	American Cyanamid	1938.6	6
7	Celanese	1697.0	7
8	Hercules	1281.0	8
9	National Distillers	1132.6	11
10	Rohm & Haas	1102.9	9

Earnings[a]

	$ Millions	Rank 1983
Monsanto	$320.0	1
Dow Chemical	306.6	2
Union Carbide	233.0	3
PPG Industries	160.2	4
American Cyanamid	113.9	7
Rohm & Haas	108.2	5
W. R. Grace	103.4	6
Hercules	101.1	8
Celanese	91.0	19
Air Products	74.8	9

Profitability

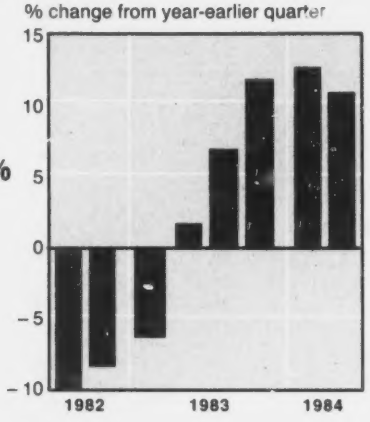
	Earnings as % of sales	Rank 1983
International Flavors	15.7%	1
Freeport-McMoRan	11.4	3
Loctite	11.3	4
Nalco Chemical	10.8	2
Rohm & Haas	9.8	6
Monsanto	9.1	9
Lubrizol	8.9	7
Petrolite	8.4	5
First Mississippi	8.4	12
Air Products	8.3	10

a After taxes. **Note:** Based on 30 companies listed on page 14.

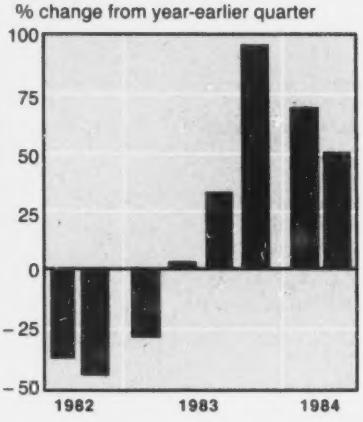
Chemical industry 1984 second-quarter results

- Sales up 11%
- Earnings climb 52%
- Profit margins rise to 6.2%
- Production up 8%
- Prices increase 4%

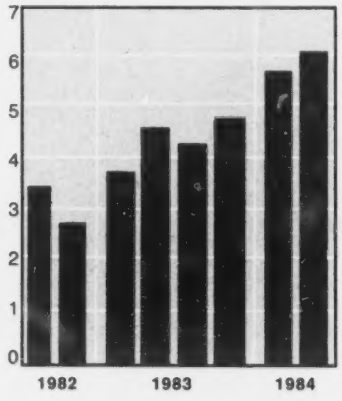
Sales
% change from year-earlier quarter



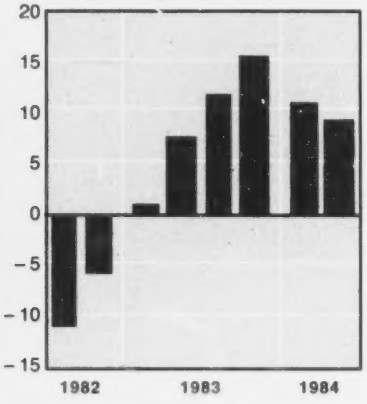
Earnings
% change from year-earlier quarter



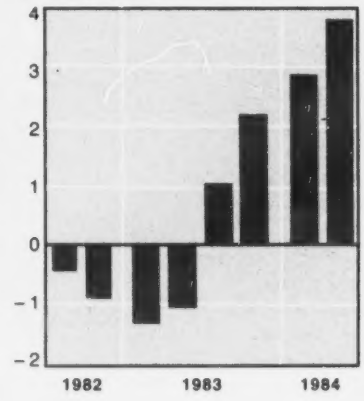
Profit margins
After-tax earnings as % of sales



Production
% change from year-earlier quarter

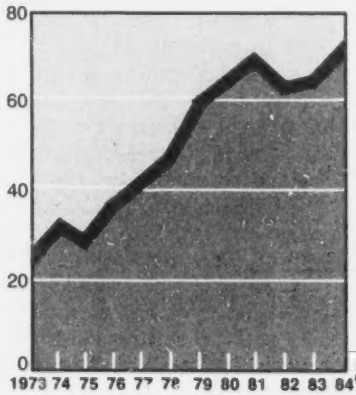


Prices
% change from year-earlier quarter

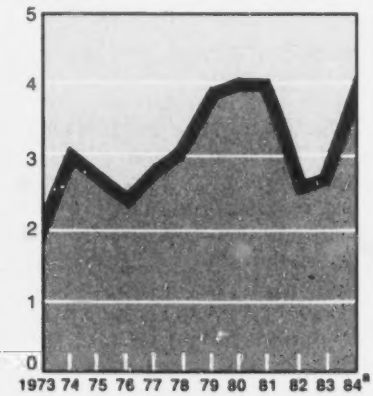


Sales in 1984 will increase 12% and earnings will be up 45% from last year, boosting profitability markedly

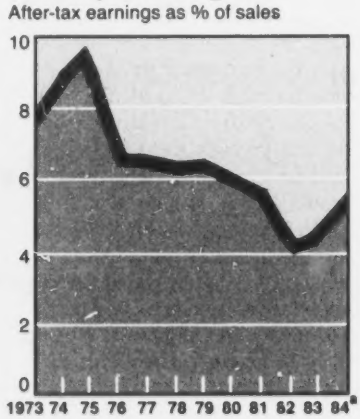
Annual sales
$ Billions



Annual earnings
$ Billions



Annual profit margins
After-tax earnings as % of sales



a C&EN estimates. **Note:** All sales, earnings, and profit-margin data are based on combined results of the 30 companies listed on page 14.

Earnings of major chemical companies rose 52% on 11% sales increase

	SECOND-QUARTER 1984						FIRST-HALF 1984			
	Sales	Earnings[a]	Change from 1983		Profit margin[b]		Sales	Earnings[a]	Change from 1983	
	($ millions)		Sales	Earnings	1984	1983	($ millions)		Sales	Earnings
Air Products	$ 448.9	$ 38.2	10%	46%	8.5%	6.4%	$ 901.0	$ 74.8	8%	42%
American Cyanamid	1,000.0	57.4	11	34	5.7	4.8	1,938.6	113.9	13	62
Celanese	860.0	47.0	3	124	5.5	2.5	1,697.0	91.0	6	237
Chemed	85.9	6.1	32	24	7.1	7.5	167.3	11.1	33	29
Crompton & Knowles	62.6	2.4	3	14	3.8	3.5	122.4	4.2	6	24
Dow Chemical	2,986.0	184.6	9	98	6.2	3.4	5,902.0	306.6	12	89
Essex Chemical	57.0	3.3	25	371	5.8	1.5	101.0	5.2	16	126
Ethyl	446.5	31.8	0	21	7.1	5.9	864.5	56.5	2	22
First Mississippi	85.8	8.4	34	87	9.8	7.0	157.9	13.2	42	113
Freeport-McMoRan	217.8	25.9	17	24	11.9	11.2	420.5	47.9	8	14
H. B. Fuller	117.3	4.0	9	9	3.4	3.4	222.1	6.1	11	11
W. R. Grace	1,741.4	57.4	8	42	3.3	2.5	3,238.7	103.4	9	40
Hercules	662.0	53.4	16	44	8.1	6.5	1,281.0	101.1	15	57
International Flavors	130.9	21.2	4	1	16.2	16.6	254.5	40.0	3	2
International Minerals	469.8	25.2	8	80	5.4	3.2	858.6	52.0	7	48
Loctite	63.6	7.6	11	46	11.9	9.1	126.2	14.2	12	42
Lubrizol	222.7	21.6	5	18	9.7	8.7	431.4	38.5	9	31
Monsanto	1,801.0	145.0	12	38	8.1	6.5	3,533.0	320.0	14	57
Morton Thiokol	522.5	26.2	17	33	5.0	4.4	1,063.8	54.9	19	27
Nalco Chemical	183.4	20.4	12	11	11.1	11.2	358.9	38.7	11	11
National Distillers	539.4	12.2	12	10	2.3	2.3	1,132.6	47.6	23	74
Olin	545.3	33.0	11	38	6.1	4.9	1,071.8	60.2	11	29
PPG Industries	1,100.0	86.1	18	37	7.8	6.8	2,100.0	160.2	17	69
Pennwalt	272.5	11.6	11	68	4.3	2.8	530.0	21.0	9	59
Petrolite	70.4	6.0	−3	9	8.5	7.6	143.2	12.0	−1	1
Reichhold Chemicals	219.1	7.9	12	20	3.6	3.4	428.4	13.4	15	25
Rohm & Haas	554.8	51.9	6	20	9.4	8.3	1,102.9	108.2	12	41
Stauffer Chemical	390.9	14.1	31	def	3.7	def	799.7	30.1	22	110
Union Carbide	2,403.0	126.0	10	103	5.2	2.8	4,796.0	233.0	10	112
Witco Chemical	382.5	16.2	11	31	4.2	3.6	749.2	30.9	12	34
Total 15 largest companies	**$16,080.6**	**$ 975.4**	**10%**	**55%**	**6.1%**	**4.3%**	**$31,481.5**	**$1883.4**	**12%**	**66%**
Second 15 companies	**$ 2,552.4**	**$ 176.7**	**14%**	**38%**	**6.9%**	**5.7%**	**$ 5,012.7**	**$ 326.5**	**13%**	**28%**
GRAND TOTAL	**$18,633.0**	**$1152.1**	**11%**	**52%**	**6.2%**	**4.5%**	**$36,494.2**	**$2209.9**	**12%**	**59%**

a Earnings from operations excluding major nonrecurring and extraordinary items. b Earnings as a percentage of sales. def = deficit.

cial construction have pushed ahead, although there are signs of slowing as higher interest rates put a squeeze on home buying. Agricultural markets also have been up from a year ago, as the government ended its payment-in-kind crop setaside program, and farm income was high enough to support buying this year.

There is still room for expansion, however, as U.S. exports of chemicals have shown no signs of increasing in the face of the strong dollar, compared to foreign currencies. And this same strong dollar is making foreign-made chemicals cheaper, increasing imports into this country and crowding some chemical markets.

Nonetheless, expanding demand for chemicals pushed production up about 8% in the second quarter over the same period a year ago. This represents some slowdown in the growth rate, though, as chemical production in the first quarter was up 11% from the same period the year before, according to government figures. And it is just about half the almost 16% rise in output registered in fourth-quarter 1983.

Chemical prices also started to pick up more in the second quarter after languishing from the effects of the recession. According to the government's producer price index, prices for chemicals and allied products in the second quarter averaged 3.8% higher than in second-quarter 1983. This represents an increase in the chemical inflation rate since the first quarter, when prices were up 2.9% from a year before.

An examination of the second-quarter results shows that the larger, more basic-chemical-oriented firms surpassed the smaller firms in earnings performance, but not in profitability. Sales for the 15 larger firms increased 10% to a total of $16.1 billion. For the 15 smaller firms, sales rose 14% to total $2.6 billion. However, combined earnings for the 15 larger firms increased 55% to $975 million, whereas earnings for the smaller firms rose 38% to $156 million. Thus, profit margins (earnings as a percentage of sales) for the larger firms averaged 6.1%, up from 4.3% a year ago. For the small-

FIRST-HALF 1984		12-MONTH RUNNING DATA			
Profit margin[b]		Change from 1983		Profit margin[b]	
1984	1983	Sales	Earnings	1984	1983
8.3%	6.3%	7%	42%	8.0%	6.0%
5.9	4.1	9	61	5.6	3.8
5.4	1.7	11	def	5.2	def
6.6	6.9	25	23	6.4	6.5
3.4	3.0	9	39	3.0	2.3
5.2	3.1	12	144	4.1	1.9
5.1	2.6	19	25	3.6	3.4
6.5	5.5	8	24	6.7	5.8
8.4	5.6	32	11	5.9	7.0
11.4	10.8	6	0	12.0	12.7
2.7	2.7	16	39	3.2	2.7
3.2	2.5	8	2	2.7	2.9
7.9	5.8	10	71	7.2	4.7
15.7	15.9	3	−8	14.8	16.5
6.1	4.4	4	26	6.6	5.5
11.3	8.9	12	54	10.9	7.9
8.9	7.5	6	24	8.0	6.8
9.1	6.6	11	56	7.4	5.3
5.2	4.8	33	64	6.4	5.2
10.8	10.8	8	11	10.5	10.3
4.2	3.0	33	40	3.1	3.0
5.6	4.8	13	33	4.2	3.5
7.6	5.3	17	55	7.4	5.6
4.0	2.7	9	158	5.2	2.2
8.4	8.3	−1	−12	7.7	8.7
3.1	2.9	6	93	3.0	1.7
9.8	7.8	10	60	8.7	6.0
3.8	2.2	10	−81	0.5	2.6
4.9	2.5	7	92	4.0	2.2
4.1	3.5	13	52	4.1	3.0
6.0%	**4.0%**	**11%**	**70%**	**5.2%**	**3.4%**
6.5%	**5.7%**	**10%**	**14%**	**5.9%**	**5.7%**
6.1%	**4.3%**	**11%**	**59%**	**5.3%**	**3.7%**

er companies, profit margins averaged 6.9%, up from 5.7% in second-quarter 1983.

As in recent quarters, to get these higher margins all 30 companies had to rely on more than just increased sales: Lower operating costs and improved efficiencies once again came into the picture. Celanese chairman, president, and chief executive officer John D. Macomber says of that company's 124% increase in earnings in the quarter, "Strong demand for many of our products helped us achieve this record. We also benefited from our own efforts over the past two years to permanently reduce our costs of doing business."

And Du Pont chairman Edward G. Jefferson says, "Second-quarter results reflect the continued strength of the domestic economy and the benefits of productivity and product quality improvement programs."

Add to these imposed efficiencies and cost-cutting measures the natural efficiencies gained from higher plant operating rates that follow from increased demand, and the potential for higher earnings leverage becomes clear.

Most of the trends derived from the figures for the 30 chemical companies for the second quarter also hold true for the first half. For the entire group, earnings in the first six months increased 59% from last year's first half to a total of $2.21 billion. Sales increased 12% to $36.5 billion. And profit margin rose to 6.1% from 4.3% in first-half 1983.

In comparisons by company size, the larger 15 companies outperformed the 15 smaller ones in terms of earnings growth, but lagged in sales increase and profitability. Sales for the larger companies increased an average of 12% to total $31.5 billion, and sales of the smaller firms rose an average of 13% to total $5.01 billion. On the other hand, earnings for the larger firms grew an average of 66% to total $1.88 billion, and those for the smaller companies gained 28% to total $327 million. Thus, profit margins for the larger companies averaged 6.0% in the first half, up from 4.0% a year earlier, but those for the smaller companies averaged 6.5%, up from 5.7% in first-half 1983.

In spite of the slowing in the annual growth rates in the second quarter from the first, the quarter-to-quarter results for the second quarter all showed improvement over the first quarter. For instance, second-quarter sales for the 30 firms increased an average of 3% from the first quarter, with those of the larger firms up 3% and the smaller firms 4%. Earnings for the entire group rose 11%; those of the larger firms increased 10%; and those of the smaller companies 18%. As a result, overall profit margin for the firms rose to 6.2% from 5.7%; that for the larger firms to 6.1% from 5.7%; and for the smaller firms to 6.9% from 6.1%.

The greater demand for chemical products in the second quarter was fairly widespread, according to company reports. But one of the big boosts in basic chemicals was in petrochemicals. This is amply evident in the chemical (largely petrochemical) earnings performance of some of the major oil companies.

For five of the oil producers—Exxon, InterNorth, Mobil, Shell Oil, and Standard Oil (Ind.)—chemical net earnings increased an average of 189% in the second quarter to a total of $279 million. Leading this group was a more than 10-fold increase at Shell to $58 million, followed by a 243% increase at Mobil to $24 million, a 194% increase at InterNorth to $5 million, and a 155% increase at Exxon to $135 million. Chemical earnings at Standard Oil (Ind.) climbed 91% to $57 million.

The increase for four of the firms, excluding Indiana Standard, for the first six months was even better, averaging 263% from first-half 1983 to a total of $377 million. Mobil climbed out of the red ink and recorded a profit of $32 million on its chemical operations. InterNorth's chemical earnings were up 444% to $10 million; Shell's increased 229% to $79 million; and Exxon's tripled to $256 million.

In its earnings statement, Mobil said of its chemical earnings performance, "The improvement reflected higher margins and volumes, particularly in petrochemicals, stemming from improved economic conditions and the benefits of major facilities expansions." And Shell Oil president John F. Bookout says, "The major reason for these encouraging earnings gains was sharply higher sales volumes."

The improvement in earnings extended further downstream and more broadly than just the basic petrochemicals, however. Celanese's

Earnings up substantially at both oil and diversified companies

	% chemical sales	SECOND-QUARTER 1984 Sales ($ millions)	Earnings[a] ($ millions)	Change from 1983 Sales	Change from 1983 Earnings	Profit margin[b] 1984	Profit margin[b] 1983	FIRST-HALF 1984 Sales ($ millions)	Earnings[a] ($ millions)	Change from 1983 Sales	Change from 1983 Earnings	Profit margin[b] 1984	Profit margin[b] 1983
OIL AND GAS COMPANIES													
American Petrofina	15%	$ 498.9	$ 15.7	−16%	83%	3.1%	1.5%	$ 1,046.8	$ 26.0	3%	192%	2.5%	0.9%
Atlantic Richfield	10	6,341.6	406.3	−3	3	6.4	6.0	13,083.9	801.4	2	11	6.1	5.6
Chevron	4	7,630.0	378.0	9	22	5.0	4.4	14,900.0	758.0	6	12	5.1	4.8
Diamond Shamrock	23	1,130.0	64.3	15	144	5.7	2.7	2,272.1	123.8	24	301	5.4	1.7
Exxon	7	24,307.0	1350.0	6	26	5.6	4.7	49,213.0	2825.0	6	32	5.7	4.6
InterNorth	7	1,696.8	50.7	60	57	3.0	3.0	3,696.6	184.2	53	37	5.0	5.5
Kerr-McGee	13	905.4	38.0	8	1	4.2	4.5	1,804.1	78.3	7	27	4.3	3.6
Mobil	4	14,896.0	366.0	3	−9	2.5	2.8	29,921.0	746.0	4	14	2.5	2.3
Occidental Petroleum	10	3,791.0	125.0	−18	1090	3.3	0.2	7,664.1	231.6	−19	536	3.0	0.4
Phillips Petroleum	16	4,050.0	220.0	7	61	5.4	3.6	8,010.0	413.0	8	83	5.2	3.0
Shell Oil	16	5,622.0	418.0	10	7	7.4	7.6	10,811.0	743.0	9	17	6.9	6.4
Standard Oil (Ind.)	10	7,400.0	524.0	0	23	7.1	5.8	15,000.0	1118.0	1	36	7.5	5.5
Standard Oil (Ohio)	5	3,282.0	458.0	6	−4	14.0	15.3	6,206.0	839.0	6	1	13.5	14.1
Sun	3	3,950.0	137.0	4	1	3.5	3.6	8,160.0	280.0	9	24	3.4	3.0
Tenneco	7	3,791.0	220.0	6	7	5.8	5.7	7,668.0	375.0	7	19	4.9	4.4
Texaco	4	10,500.0	302.0	6	−8	2.9	3.3	20,400.0	623.0	1	−4	3.1	3.2
Unocal (Union Oil)	11	3,000.0	185.7	7	33	6.2	5.0	5,680.0	365.8	8	37	6.4	5.1
DIVERSIFIED MANUFACTURERS													
Allied	23	2,793.0	130.0	10	10	4.7	4.7	5,596.0	263.0	11	23	4.7	4.3
Aluminum Co. of America	11	1,452.3	112.8	15	226	7.8	2.8	2,935.7	210.6	22	937	7.2	0.8
Beatrice Foods	5	2,207.0	72.0	−4	−5	3.3	3.3	4,438.0	150.0	−3	−4	3.4	3.4
Borden	18	1,186.5	51.3	9	12	4.3	4.2	2,282.8	85.2	13	25	3.7	3.4
Borg-Warner	24	1,034.7	70.8	17	57	6.8	5.1	1,982.5	121.0	17	50	6.1	4.8
Du Pont	36	9,118.0	437.0	3	61	4.8	3.1	18,371.0	810.0	5	71	4.4	2.7
Eastman Kodak	23	2,556.0	229.3	7	35	9.0	7.1	4,696.8	387.1	4	77	8.2	4.8
Engelhard	13	606.0	19.9	−2	11	3.3	2.9	1,248.7	39.9	2	17	3.2	2.8
FMC	38	939.8	64.6	7	66	6.9	4.4	1,893.2	107.1	9	52	5.7	4.1
General Electric	13	6,664.0	579.0	−1	11	8.7	7.7	13,247.0	1064.0	3	12	8.0	7.4
Georgia-Pacific	11	1,823.0	84.0	7	50	4.6	3.3	3,454.0	135.0	11	57	3.9	2.8
B. F. Goodrich	41	883.4	32.4	11	431	3.7	0.8	1,700.0	42.3	13	def	2.5	def
Kaiser Aluminum	19	988.8	32.5	28	def	3.3	def	1,775.0	47.1	30	def	2.7	def
Koppers	34	463.5	14.7	23	145	3.2	1.6	810.4	11.2	22	def	1.4	def
Eli Lilly	24	723.9	105.2	−2	3	14.5	13.8	1,618.7	251.9	3	6	15.6	15.1
3M	15	1,959.0	193.0	10	14	9.9	9.5	3,834.0	368.0	10	13	9.6	9.4
Merck	19	891.3	131.4	8	7	14.7	15.0	1,739.9	256.5	9	8	14.7	14.9
NL Industries	36	359.2	4.1	4	def	1.1	def	683.0	5.0	−5	def	0.7	def
Northwest Industries	24	496.2	23.1	23	7600	4.7	0.1	944.1	37.7	28	1994	4.0	0.2
Pfizer	11	985.7	118.1	7	11	12.0	11.6	1,905.5	245.8	4	13	12.9	11.9
Tyler	32	245.8	8.6	36	87	3.5	2.6	462.7	12.6	34	94	2.7	1.9
Uniroyal	31	614.6	36.0	13	84	5.9	3.6	1,154.5	53.1	16	129	4.6	2.3
U.S. Steel	6	4,900.0	113.0	11	def	2.3	def	9,700.0	284.0	17	def	2.9	def
Upjohn	16	581.7	47.6	12	8	8.2	8.5	1,144.7	112.7	14	26	9.8	8.9
Vulcan Materials	31	259.2	25.6	30	66	9.9	7.7	461.5	32.3	30	111	7.0	4.3

a From continuing operations excluding nonrecurring and extraordinary items. b Earnings as a percentage of sales. def = deficit.

Macomber says: "Fibers accounted for the largest share of second-quarter income, reflecting strong demand for industrial products and polyester staple." Net income for fibers at the company increased 47% in the second quarter to $1.66 per share, or about $30 million.

Monsanto's fibers and intermediates operations also did well with pretax earnings rising 57% to $33 million in the second quarter from a year earlier. For the six months, Monsanto's fibers and intermediates operations gained 143% in pretax earnings to $70 million. These results came on sales increases of 7% for the quarter to $337 million and 17% for the half to $652 million.

At Du Pont, fibers after-tax earnings in the second quarter increased just 11% to $102 million on a sales decline of 1% to $1.21 billion. This

represents a considerable slowing from the first quarter and gives an annual increase for the first six months of 1984 of 5% in sales to $2.41 billion and a 38% rise in earnings to $204 million.

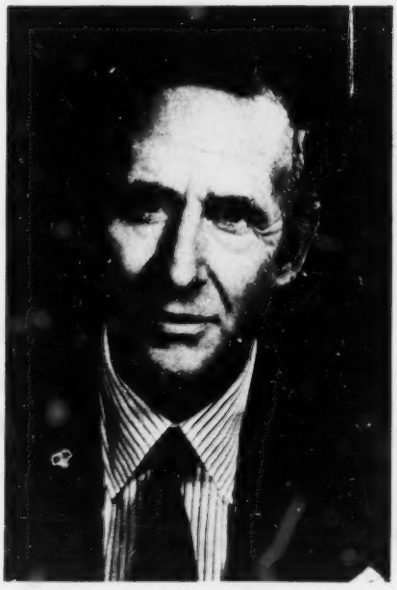
Products that go into petrochemicals also did well in the quarter. At Witco Chemical, whose earnings increased 31% in the second quarter, chairman William Wishnick attributed the results to "higher volume and stronger margins, particularly in those divisions supplying specialty chemicals to the plastics industry."

Specialty chemicals also did well at B. F. Goodrich, for which that business segment had operating income of $23 million in the second quarter, up 45% from last year. But polyvinyl chloride was the best performer for Goodrich; its pretax income rose to $28.2 million from only $2.4 million in the second quarter last year—a 1075% jump.

Agricultural chemicals—both herbicides and fertilizers—with the end of the PIK program did well. W. R. Grace says that its 42% increase in earnings in the second quarter was attributable mainly to the performance of its agricultural chemicals group, which earned $14 million in the quarter, compared with $1.6 million in the second quarter of 1983. Grace says that historically the second quarter is the strongest period for fertilizer sales, but last year's second quarter was unusually weak because of the PIK program.

At Williams Cos., Agrico Chemical's second-quarter operating profit jumped to $26.6 million from $3.3 million in the same period last year. Chairman Joseph H. Williams says, "Fertilizer volumes rose 34% above the second quarter last year, and shipments of phosphate rock increased by 9% in the same period. Prices for virtually all nitrogen and phosphate fertilizer products were also up from the same period of last year, even though phosphate margins came under severe pressure because of the late, wet spring in the U.S."

International Minerals & Chemical president George D. Kennedy says that the 35% increase in earnings from continuing operations reflects better volume in fertilizer tonnage shipped to domestic and export markets during the past year. However, "fertilizer volume recovery did not translate into appreciably higher price for most products." he says. "Return to adequate pricing for potash and phosphate, IMC's principal products, is being constrained by high value of the dollar, financial problems in developing countries, and slow recovery of farms everywhere."



Macomber: strong demand for fibers

American Cyanamid chairman, president, and chief executive officer George J. Sella Jr. says that sales and earnings of the agricultural group were significantly higher, reflecting the continuing farm recovery in the U.S.

Kennedy: better volume in fertilizer

Monsanto's operating income from its agricultural and nutritional products unit, which is made up largely of herbicides, rose 39% to $138 million in the second quarter on a sales increase of 24% to $406 million. This occurred in spite of Monsanto's statement that it held up well last year in the face of the PIK program. President and chief executive officer Richard J. Mahoney says, "Roundup and Lasso herbicides are on schedule for another good year, with favorable market performance for both herbicides." He says of the second quarter, "Demand was aided substantially by higher acreage plantings in the U.S. and generally good weather conditions around the world for the application of these two widely used products."

While glamor products such as pesticides were doing well, some other chemicals that traditionally have rather lackluster performances also were coming out of the doldrums. Chief among these seemed to be chlor-alkalies. Pennwalt chairman and chief executive officer Edwin E. Tuttle says, "I am pleased to report that caustic soda prices in the long-depressed chlor-alkali business have finally firmed. This is long overdue and we will begin to benefit from this price relief effective with the second quarter."

PPG Industries chairman L. Stanton Williams says that chlorine demand strongly led the chemical sales recovery during the quarter. Olin also singles out chlorine as having greater demand in the second quarter.

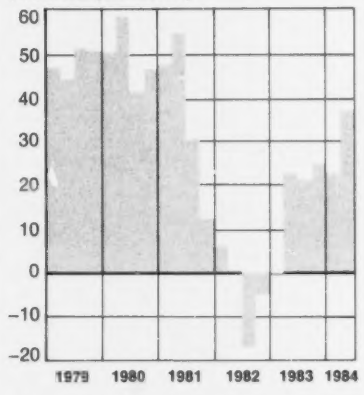
For the remainder of the year, it probably will be more of the same, although the earnings increases for chemical companies will continue to trail off as they go up against stronger 1983 quarters. However, if the U.S. markets continue to be strong, and there is further recovery in overseas markets, U.S. chemical companies will show significant earnings gains this year, perhaps as much as 40% or more. It is far from impossible. □

Profits Up Sharply for Canadian Chemicals

First-half results of most Canadian chemical companies continue to reflect the broad-based recovery in Canada's economy. Six-month sales are up substantially over last year and earnings have increased dramatically.

Much of the gain came in the second quarter. One indicator: Combined earnings of the four publicly reporting companies charted by C&EN (C-I-L Inc., Celanese Canada, Du Pont Canada, and Union Carbide Canada) hit $37.2 million (Canadian dollars throughout) in the second quarter. That's 65% better than the previous quarter, 67% ahead of the second quarter of 1983, and it is the highest quarterly earnings chalked up by the "Big Four" since the second quarter of 1981. Their combined sales, at $943 million, also was the best since the second period of 1982.

Combined second-quarter earnings pushed up 37%



a After-tax earnings of four largest publicly reporting Canadian chemical companies—Celanese Canada, C-I-L, Du Pont Canada, and Union Carbide Canada.

These combined results, however, mask some big differences in the performance of various companies. Although C-I-L and Celanese boosted their first-half earnings a hefty 58% and 49%, respectively, Du Pont's earnings soared 120%. And Union Carbide turned a $9 million loss in last year's first half into a $4.8 million profit this year.

Despite its apparent good fortune, Carbide still has its share of problems. The company's net income included its $8 million share of government assistance given to Petromont, the troubled, Montreal-based basic petrochemical producer that Carbide owns along with the Quebec government. That was a big factor in Carbide's $14 million turnaround in first-half earnings.

Company chairman W. Norman Kissick continues to complain about the devastating impact of taxes on feedstock and raw materials on Carbide's earnings. And, although Carbide's first-half sales increased 8% to $353 million, depressed prices in world petrochemical markets continue to be a "major earnings detractor," says Kissick.

But Du Pont Canada's president and chief executive officer, J. Edward Newall, credits higher selling prices in both the export and domestic markets for his firm's 6.5% rise in second-quarter sales to $312 million. Six-month sales rose 11% to almost $609 million. Newall says that volume was level with last year as weak demand for nylon carpet and apparel fibers was offset by a good show of strength in consumer and industrial packaging markets. Sales of polyethylene pipe and explosives to the mining sector also were brisk.

For Celanese Canada, sales and net income in the second quarter improved only narrowly over the same period in 1983. Sales in the second quarter were up 7.8% to $107 million, but that still was better than the firm's first-quarter performance.

Celanese's earnings record, however, is a different story. Net earnings jumped 107% in the first quarter, but only 14% in the second.

C-I-L's earnings, on the other hand, were much stronger in the second quarter than in the first. The company earned $16.9 million on sales of $339 million in the March-June period, but earned only $5.2 million on sales of $284 million in the first quarter.

C-I-L president and chief executive officer C. H. Hantho notes that although gains in selling prices have been only modest, increased sales volume and productivity gains helped to improve operating results. Plastics sales were well ahead of 1983 as additional output became available from the expanded Edmonton plant.

Although pleased with their results so far this year, Canadian chemical companies are guarded about prospects for the rest of the year. Telltale signs of a slowdown in the Canadian economy are becoming apparent. Du Pont's Newall says, for instance, that he doesn't expect second-half results to match those of the first six months.

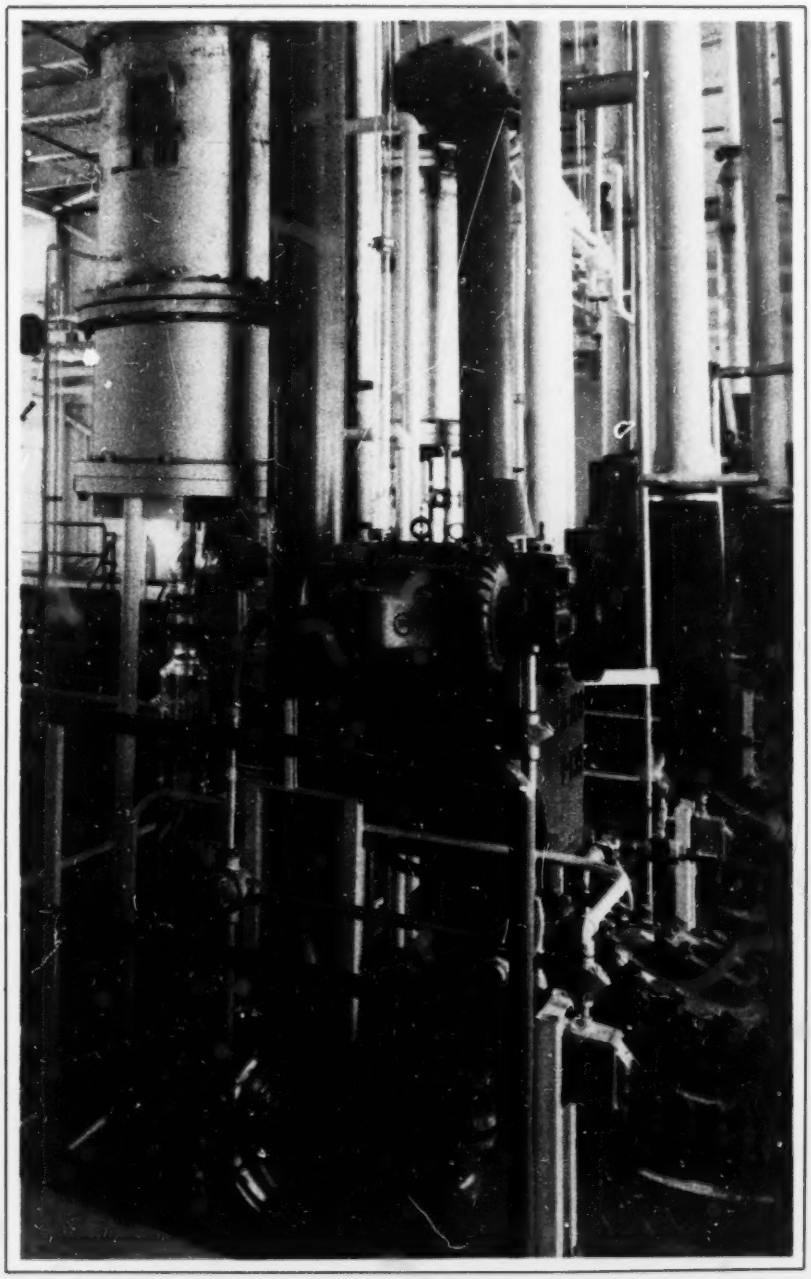
Earl Anderson, New York

First-half sales, earnings increased markedly

	FIRST-HALF 1984					
$ Millions (Canadian)	Net sales	Change from 1983	Net income[a]	Change from 1983	Profit margin[b] 1984	1983
C-I-L Inc.	$ 623.6	8.1%	$22.1	57.9%	3.5%	2.4%
Celanese Canada	206.4	6.7	5.5	48.7	2.7	1.9
Du Pont Canada	608.7	11.4	27.5	120.0	4.5	2.3
Union Carbide Canada	353.5	8.2	4.8	c	1.4	c
TOTAL	$1792.2	9.0%	$59.9	182.6%	3.3%	1.3%

a Net income from continuous operations, excluding extraordinary gains or losses. b Net income as percentage of sales. c Deficit in 1983.

Custom Synthesis Expanding for Drugs and Intermediates



Reactors used for custom synthesis at Ganes Chemicals' Pennsville, N.J., plant

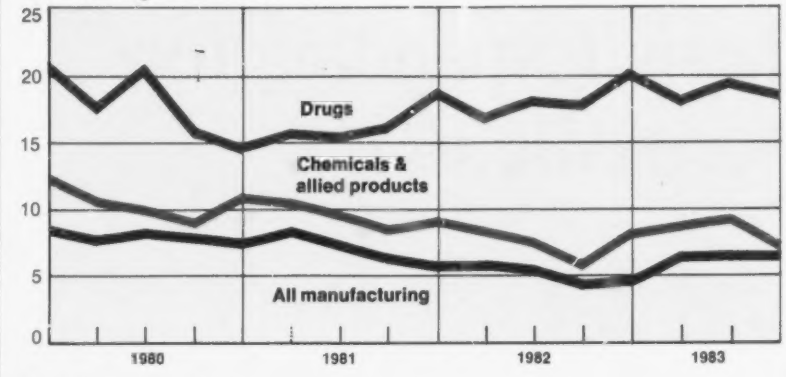
Stephen C. Stinson, C&EN New York

A 13% expansion of U.S. drug and related product sales to $33 billion this year will boost the fortunes not only of domestic drug companies but of the hundreds of firms that custom-make intermediates and bulk drugs for these companies.

Many drug companies try to produce all their needs themselves. Even at the largest drug firms, however, there may be shortages of capacity at the preparations laboratory, pilot plant, or full-scale plant. Or there may be reactions that drug companies consider too complex or dangerous. Thus, in addition to producing generic drugs such as phenobarbital or such intermediates as 6-aminopenicillanic acid to sell to many drug companies, there is a thriving if risky business for those firms making intermediates and bulk drugs that are unique to one customer.

Firms that do custom synthesis for individual drug companies come in all shapes and sizes. For example, tiny but capable firms such as Carbolabs of New Haven, Conn., and Marshalltown Laboratories of Winston-Salem, N.C., can run three 22-L flasks side by side to make a year's supply of 5 to 25 kg of an intermediate for a drug that is in its early stages of development. At the other end of the scale, dedicated units at such companies as Ethyl Corp. at Baton Rouge, and Tennessee Eastman at Kingsport, Tenn., turn out the 3000 to 5000 kg per

Profitability of U.S. drug sales leads that of all industry



Source: Bureau of the Census

year that an average drug needs that has just hit its marketing stride.

The world of custom synthesis is aswirl with changes. Some companies get fed up with juggling the many projects needed to succeed and turn their backs on it. Others see great potential in the business and can't wait to elbow their way in.

Among the firms that have had second thoughts about custom synthesis are Syntex Chemicals, J. T. Baker Chemical, Parke-Davis division of Warner-Lambert, and Pfizer.

Syntex Chemical began its cutback three years ago. The company still seeks business in custom synthesis, according to sales manager Al Wilson, but only where it is a good fit in chemistry and equipment. Much of the capacity once used for custom synthesis has been devoted to needs of the parent drug company, Syntex Corp.

J. T. Baker got into custom synthesis in 1981 as a way to use capacity freed after its parent company, now called Richardson-Vicks, sold Merrell Pharmaceutical to Dow. But a spokesman for Baker says that the company now prefers to use the capacity for its own product line, which it sells to many customers, rather than be dependent on the downstream fortunes and marketing abilities of one customer. The company still produces for a few selected customers but does not seek new business.

Similar thinking guided Parke-Davis, says marketing and new product planning manager John Controulis. The company hoped for long-term contracts for custom synthesis, he says, but these never developed. Thus, although the company's contracts of 50 to 200 kg per year of drug, food, and cosmetics compounds were profitable, the question arose of how best to use available capacity. Seeing a few of its own new drugs in the pipeline, and wishing to make sure enough capacity would be available for them, Parke-Davis stopped serving all but one isolated customer in July.

But sometimes the withdrawal of one firm can mean the appearance of another. Pfizer spun off its special chemicals department in Greensboro, N.C., to a group of its employees in April. The main business of what is now Morflex Chemical Co. is vinyl plasticizers. But president Gary F. Taft says that the new firm also makes a few custom ester drug intermediates. Another of the company's specialties for the drug industry is custom sulfonation of aromatics followed by alkali fusion to phenols.

Albany International also sold off its chemicals division in Columbus, Ohio, to Essex Chemical Corp. in 1983. Essex was attracted by the division's custom synthesis business, which it hoped to use to get into the field. Albany originally bought the division as Chemsampco to make insect pheromones to go with its pheromone dispensing technology but found it not very profitable.

All segments of U.S. drug market are growing

$ Millions	U.S. consumption	Exports	Imports
ANTIBIOTICS			
1982[a]	$ 1,820	$ 730	$ 160
1981	1,560	710	180
1980	1,330	640	120
1979	1,100	530	120
1978	1,030	450	110
BIOLOGICALS			
1982	1,250	430	30
1981	1,200	360	30
1980	1,070	370	20
1979	930	280	10
1978	850	170	10
CENTRAL NERVOUS SYSTEM DRUGS			
1982	4,020	100	130
1981	3,490	120	120
1980	3,090	90	120
1979	2,930	70	80
1978	2,490	80	80
ENZYMES AND FERMENTS			
1982	320	40	90
1981	310	40	90
1980	270	40	70
1979	250	40	60
1978	230	40	50
HORMONES			
1982	$ 1,150	$ 210	$ 80
1981	980	210	70
1980	850	190	60
1979	790	170	50
1978	780	160	50
VITAMINS			
1982	1,580	110	150
1981	1,440	90	190
1980	1,380	70	160
1979	1,230	60	150
1978	1,030	60	140
OTHER[b]			
1982	14,690	710	400
1981	12,650	670	370
1980	10,600	610	400
1979	9,510	510	420
1978	9,460	530	420
TOTAL[c]			
1982	$24,830	$2320	$1050
1981	21,610	2230	1050
1980	18,620	2000	960
1979	16,740	1660	890
1978	15,880	1480	860

a Latest year for which data are available. b Includes anti-infective, gastrointestinal, autonomic, cardiovascular, hematological, and anticancer drugs; antihistamines; and smooth-muscle relaxants. c Items may not add to totals because of rounding. **Source:** U.S. International Trade Commission

Essex has re-erected the division as its custom synthesis subsidiary, Orsynex, and installed Kenneth Houle as president. Houle emphasizes that he operates at arm's length from another newly acquired Essex subsidiary, Pioneer Pharmaceuticals, makers of generic drugs. Drug companies are sometimes reluctant to reveal details of new drug candidates to custom manufacturers who are too closely tied to other drug companies.

Another new entrant to custom synthesis is Union Carbide Corp. The company's process systems and services department will use the preparations laboratories and pilot plant at South Charleston, W.Va., to make amounts ranging from kilograms to tons. Carbide business manager B. I. "Woody" Friedlander estimates that the total U.S. market for custom synthesis is $500,000 per year, with an annual growth rate of 8 to 12%. Of this amount, drugs, pesticides, and their intermediates comprise perhaps 85 to 90%, with drugs and their intermediates slightly greater.

This relatively large market and growth rate for custom synthesis has not escaped the notice of European and Japanese chemical companies. Market researchers at Eastman Kodak say the U.S. market for such services is larger than in other areas of the world and growing at a faster rate. This situation, combined with a strong U.S. dollar that cheapens imports, has led foreign suppliers to add sharp price competition to their long-standing aggressiveness based on quality.

Foreign firms market custom synthesis in the U.S. through their U.S. subsidiaries or through agencies. For example, Mobay Chemical Corp. offers custom synthesis domestically and can refer projects to its parent, Bayer of West Germany. Peter Benzing, general manager of Mobay's organic and rubber chemicals division, says the tie with Bayer gives drug firms the two sources of supply desired for intermediates going into commercial drugs. It also gives multinational drug firms sources of supply on two continents.

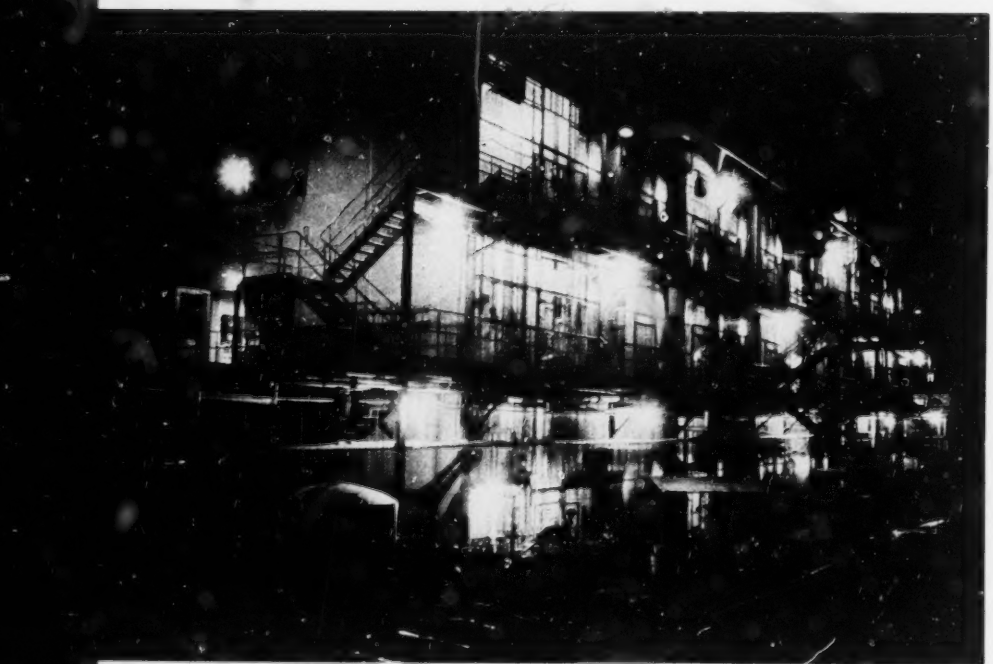
Among agents that represent foreign firms are Henley & Co., New York City, and S.S.T. Corp., Clifton, N.J. Both companies also have U.S. clients. Henley's overseas clients offering custom synthesis to the drug industry include Finorga of France and SSF Dottikon of Switzerland.

To be successful attracting drug industry business, a company must have capabilities to run uncommon or dangerous processes, says Lester LaGrange, Henley's manager of technical sales. For example, Finorga has a cryogenic reactor for Birch reductions and selective oxidations. SSF Dottikon does nitrations, which are dangerous on a large scale.

S.S.T. Corp. arranges custom synthesis as an offshoot of its regular business, which is distribution of imported intermediates and bulk drugs from inventories in the U.S. Faced with a request for an exotic intermediate, the company searches among its clients and other firms. Sometimes the intermediate is available commercially, a spokesman says, but so little in demand as to be unadvertised. If unavailable, S.S.T. looks for companies with the right chemistry and the willingness to make the small initial amounts needed. The hope is that these small projects will mature into big ones, and the spokesman says that S.S.T. brings four to five such projects a year to this final stage.

In a switch on the usual routine, one U.S. company plans to offer custom synthesis to the drug industry from an overseas plant. Angus Chemical Co., Northbrook, Ill., will open a $13 million plant in Ringaskiddy, Ireland, in 1985, as a joint venture owned 20% by Isochem of France. Angus president Wayne Chandler says the plant will be able to do such hazardous processes as bromination, high-pressure hydrogenation, nitration, phosgenation, and reactions with carbon disulfide and dimethyl sulfate. He explains that Angus decided on a joint venture route because of Isochem's process know-how and marketing skills.

The person at a drug company that all of these hotly competitive firms try to reach often has the title of director of process engineering. This director is located within the research department and manages the "prep" or "kilo lab" and the company's pilot plant. He or she guides the production of a drug candidate through the first few kilograms needed for acute and 90-day toxicity testing, gathering information to apply to pilot production. The director scales up the process to the pilot plant, if the company has one, which makes 50 to 200 kg per year for clinical tests. After as



Union Carbide's custom synthesis plant in South Charleston, W.Va.

Custom synthesis: how one drug firm would arrange it

Process engineers at drug companies have their own systems of searching for sources of bulk drugs and intermediates. Their task is often difficult, because there are many large firms that would be willing to make several kilograms and large companies interested in 1000-kg or 10,000-kg orders. Relatively few firms serve the gray area of 50- to 200-kg quantities, and their number grows smaller for unusual chemistry or complex syntheses. C&EN asked one director of process engineering to describe his system for obtaining a source to custom-synthesize a drug or intermediate. Because he names firms he would go to in his search, he asks not to be identified.

He collects literature and catalogs of chemical firms and files them by the type of chemistry each can do and compound types each works with. He has catalogs of flavor chemical producers, because the heterocyclic rings of many of these are similar to those of drugs. He collects literature from monomer producers, because the chemistry may match what he seeks.

His company's purchasing department sometimes gets involved, but the work usually falls on him. In urgent need of a few kilograms for 90-day or acute toxicity testing, he would go to Carbolabs or Marshalltown Laboratories. He also cultivates chemistry professors in his areas, because they are often willing to make 100 to 1000 g of a needed compound in a hurry.

As greater amounts of compound are needed for chronic toxicity and clinical testing, he would seek out a company whose plant is approved by FDA as following good manufacturing practices (GMP). This is because the company he chooses might end up making commercial amounts of the drug, and he could stay on with the same supplier. Such companies he mentions are Hexagon Laboratories, Johnson Matthey, Orsynex, Quality Chemical, and Upjohn.

If one or more steps in the synthesis prove too exotic or dangerous for the GMP firm, he might seek out a non-GMP company to carry the drug to an advanced intermediate and supply it to the GMP firm as raw material. At about this time, he also would communicate with all the agents he knows to let them know of his need for the intermediate. Such agents include Austin Chemical, Chemical Dynamics, Henley, Interchem, and S.S.T.

As the drug nears FDA approval, if his company decides to continue custom synthesis on a larger scale, he will try to stay with the same GMP supplier. He might go so far as to write specifications around that supplier's capabilities. But, he says, his company's purchasing department sometimes disagrees and insists on putting the project out more generally for competitive bidding.

long as 10 years, when Food & Drug Administration approval is imminent, upper management makes a decision to add units to the company's own commercial-scale plant or to assign the active drug compound to an outside vendor.

But the prep lab or pilot plant may be backed up with work. The company might not have a pilot plant. One of the intermediates may involve a dangerous reaction or such expertise as fluorine chemistry, unavailable within the company. The company might have limited or no commercial production capacity. Or management might decide not to add a dedicated, full-scale production unit until the drug has proved itself in marketing. Each of these eventualities offers opportunities to custom synthesis firms.

Directors of process engineering at drug companies are proud of being good at what they do. They stress the importance of fair dealing and constant and open communication between themselves and their suppliers of custom synthesis. LaGrange of Henley comments that, "A good manager of a kilo lab spends a quarter of his time talking to suppliers."

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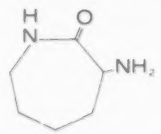

DL—, D—and L—form

* α-Amino—ε—caprolactam
* α-Methylamino—ε—caprolactam
* α-Dimethylamino—ε—caprolactam
* α-Benzylamino—ε—caprolactam

Lysine

$H_2N(CH_2)_4CHCOOH$
NH_2

DL—, D—and L-form

* *free base*
* *monohydrochloride*
* *acetate*
* *carbamate*

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Says Donald Kuhla, director of process engineering at William H. Rorer, in Fort Washington, Pa., "I try to work out a rapport, a relationship, so that [suppliers] will tell me that [they're] full-up and can't respond for two months."

For his own part, Kuhla says, "You can't shop the same project out to 12 [firms] for 50 or 100 kilos each. It's like crying 'wolf.' You can do it once or twice. [Custom synthesis firms] will try it without making any money on it, thinking to make it up later when the big orders start coming in. You only need 50 to 100 kilos a year, not only for the 10 years it takes for FDA to approve the drug, but for three to five years after that till the drug hits its market share. So people have to be convinced to go on making it for a long time in hopes of finally making money. It's very important to be up-front and honest with people, because they don't do more than cover costs."

Like most people in his position, Kuhla tries to arrange two sources of supply for security. With this, also, he stresses honest dealings. "Most drugs at maturity amount to only 3000 to 5000 kilos a year. So while the value added is high, volumes are low. We always try for two suppliers, but if the weight of the drug is only 3000 to 5000 kilos a year, you're not doing anybody a favor by qualifying more."

Factors that affect selection of a firm for custom synthesis include financial stability, past dealings, experience with the chemistry or compound type involved, reliability, fast response to a request for a price quote, and familiarity with any dangerous reactions to run them safely. If the drug company has the bulk drug made outside, it is important to have an FDA-approved laboratory from the beginning, so as not to have to shift gears at the end of development. But the most important factor is environmental. Drug companies' reputations can ride on an outside vendor's responsible disposal of waste.

"We investigate potential suppliers extensively, particularly in the environmental as well as the usual financial areas," says Robert J. Dille, director of purchasing at Eli Lilly &

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ACS division to hold symposium on custom manufacture

Both managers of process engineering for drug companies and managers of firms that offer custom synthesis find sessions of the American Chemical Society's Division of Small Chemical Businesses useful in making and keeping contacts, says Donald Kuhla, director of process engineering for William H. Rorer Inc. In this connection, the Philadelphia ACS meeting will be especially useful. The division will hold a symposium on custom manufacturing on Wednesday, Aug. 29, at 9 AM in the Civic Center.

The symposium was organized and will be chaired by J. Paul Raycob, vice president of Ennis Chemical Co. W. Bryce Anderson, president of the parent company, Ennis Industries, will speak on financial aspects. Roger L. Logan, assistant to the general manager of the chemical products division of Union Camp Corp., will give guidelines to those searching for toll producers—those who use raw materials supplied by their customers. Joseph Abelson, marketing manager for ICI America's specialty chemical division, will talk about marketing. And Nicholas Prato, manufacturing manager for McWhorter—a producer of resins for the coatings industry—will discuss manufacturing.

According to Logan, the major criteria in evaluating a toll supplier are reliability, environmental problems, and safety. He says that decisions on toll manufacturing should depend on answers to a number of questions: Have the options for making the new product in-house been thoroughly explored? Has the supplier worked on similar projects with positive results? Does the supplier have 24-hour manpower coverage for plant operations and the laboratory? Is the intended process or product proprietary or patentable? Will the toll producer try to compete in the merchant market when the contract expires? What percentage of the toll producer's capacity will be used? If the toll producer improves the process or product, who owns the improvement? Can the toll producer package the product to meet market demands?

In his presentation, McWhorter's Prato divides manufacturing into raw materials, processes to be used, and finished products. Of raw materials, Prato plans to discuss suppliers' reliability, shipping capability and lead times, and ability to maintain minimum and maximum inventories. Other important considerations include quality control tests, whether new testing equipment will be needed, logistical and regulatory aspects of handling and storage, shelf life, mutual compatibility of chemicals, proper labeling under worker right-to-know laws, and disposal of waste. When using a new raw material, the custom manufacturer must also review existing plans for such emergencies as spills.

When studying the process, Prato says, the custom manufacturer must consider its safety, time and labor requirements, time and costs of cleanups between batches, and compatibility of chemicals with equipment. For the final product, the issues are quality control, handling, legal aspects of storage, and compatibility with storage vessels.

Co. (Despite his title, Dille came up through process engineering, as did the two purchasing agents who work for him.) "Environmental concerns are what make it so hard to choose among so many companies. Small companies often don't have their own waste disposal or solvent recovery facilities. They have to send it out. That's risky. So we worry about that."

Fast response on a price quote can be important. Fast means as short as one week to study the process, decide on its feasibility, and quote a price per kilogram. Several large firms do respond rapidly, according to a number of process engineering directors. But they also point out that one large firm, otherwise favored as thorough, cautious, and reliable, could, as one director quipped, "take three months to decide whether to sign a secrecy agreement. In that time, we've got a quote from someone else, he's developed the process, and we've taken delivery on the first few kilos."

Process engineering directors don't always agree on sending work

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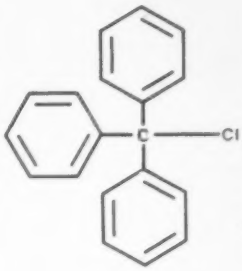

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to other drug companies. Hoechst-Roussel Pharmaceuticals, Somerville, N.J., has its cephalosporin antibiotic cafotaxime made by Baxter Travenol of Deerfield, Ill., because the company lacks a fermentation plant in the U.S. But the worldwide facilities of the parent Hoechst (of West Germany) are otherwise so vast, a spokesman says, that the New Jersey company never has to buy custom synthesis outside.

One drug company that asked not to be named has a strict rule against dealing in this way with other drug firms, unless the other firm has developed the drug, licensed it, and insisted on producing it for the first few years. Dille says that Lilly would use another drug company, subject to proper secrecy agreements, but not if the other company marketed drugs competitive with the Lilly compound. William Welstead of A. H. Robins Co. agrees that there are risks sending work to other drug companies, but adds, "These others couldn't stay in that business long without observing proper business procedures."

But these directors also agree that a company like Mobay, for example, does not count as "another drug company." They feel that Mobay operates sufficiently distant from the drug operations of Bayer and of Bayer's other U.S. subsidiary, Miles Laboratories.

There is also difference of opinion about the wisdom of dealing with overseas firms. "We've talked with representatives of European companies over the past few years," says Vasken Paragamian of McNeil Pharmaceutical, in Fort Washington, Pa., "but no projects have resulted. There are problems of communications, tariffs, and closeness. I always ask them, 'What can you offer me? Why should I do business with you?' They answer 'Quality.' But there haven't been any opportunities so far." Paragamian's concern is that detailed technical discussions are needed with an outside supplier in the first stages of process development.

That is just when companies that offer custom synthesis to the drug industry would like drug firms to bring them in—at the earliest stage of a drug's development. Their hope

is that their growing expertise in producing the drug or advanced intermediate, combined with the FDA requirement of a Drug Master File, will lock the business up for them when the drug is approved.

A Drug Master File is a document that includes descriptions of all producers that work on the drug and its intermediates, as well as all raw materials, reactions, processes, equipment, analytical procedures, and expected by-products at each step. Once an outside supplier and its process have been filed in this way, it is very difficult to change. Moreover, outside suppliers often can keep details of their process improvements secret, even from the drug company customers. Outside suppliers can patent some processes. Thus, although an outside supplier will give a Drug Master File to FDA as a part of the drug company's submissions, it can ask that the file be kept confidential, even from the company whose drug it covers.

Process improvements by outside suppliers lower their production costs of drugs and their intermediates. This cost advantage can become so great by the time FDA approves the drug that it can be difficult for a new company to compete as a second source. As Lilly's purchasing manager Dille puts it, "A competitor must have developed absolutely new chemistry to take the business away. From a purchasing standpoint, it's hard to know if you have a good deal or not, because competitive bidding is limited by the nature of the situation."

But if the earliest stages of drug development have the greatest potential for future profit from commercial-scale orders, they also pose the greatest risks. There is a certain mortality among new drug candidates and even among newly approved drugs. For example, unexpected side effects may appear at any stage. A drug may fail to live up to its market potential. Or a drug company may take production of a newly approved drug in-house. A custom supplier may not have produced enough drug or intermediate to cover process development costs.

There are different arrangements to cover process development costs. Some custom synthesis firms ask for and get advance payment for developmental work. Drug companies tend to resist this arrangement, and some directors of process engineering say they can hold out until they find a supplier willing to accept another arrangement. Still, some contracts call for a price for development and a 100-gram sample of product. For a process known only from a drug company's laboratory work that produced a few dozen grams, the drug company may agree to a fixed fee for scaleup and take whatever yield results, from 0 to 100%.

The most common arrangement,

Continued on page 52

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however, is for the custom supplier to estimate development costs and fold them into the price per kilogram over a three- to five-year contract. This can result in prices of $2000 to $10,000 per kg, but in developmental stages, drug companies are more concerned with reliable supply than price. This arrangement involves risk, however, that a project may be canceled before the custom supplier has recovered process development costs.

In such cases, Orsynex president Houle says that the drug firm usually compensates the custom synthesis firm to avoid losses. But market researcher Carol M. Apuzzi of Ganes Chemicals, New York City, says that Ganes simply runs the risk of such a loss.

Development costs of custom synthesis firms can include those for preparing the premanufacturing notice (PMN) that must be supplied to the Environmental Protection Agency under the Toxic Substances Control Act (TSCA). Research amounts of a new drug or intermediate are exempt from TSCA, but the 50 to 200 kg-per-year amounts for clinical tests require a PMN.

Philip St. George, marketing specialist at Kodak Laboratory & Specialty Chemicals, says that Kodak usually prepares the PMN and asks the drug company customer for data needed for it. He adds that Kodak also has its Safety & Human Factors Laboratory to get environmental and toxicity data that may be lacking. Benzing of Mobay says its drug company customers usually prepare the PMNs.

Drug companies differ in their needs for custom synthesis and thus in the opportunities they offer to those who purvey it. Smaller drug companies, for instance, have drug discovery research groups, kilo labs, no pilot plants, and limited or no commercial production capacity. Medium-sized companies have a pilot plant in addition. Larger companies have extensive commercial-scale plants as well.

Among the larger companies there is also the management philosophy to consider. Some large companies prefer to make everything in-house, from discovery through commercial production. Others routinely farm out advanced intermediates, because they prefer not to devote their resources to process development. After FDA approval, they might still buy the advanced intermediate outside, until the success of a drug in the marketplace justifies adding dedicated units for it to their own plants. But all large companies do the last one or two steps of drug production inside.

A. H. Robins serves as an example of how a small drug company operates. The firm produces on a commercial scale for itself through Lee Laboratories, Petersburg, Va., which it owns jointly with Boehringer Ingelheim of West Germany. Of the two dozen organic active

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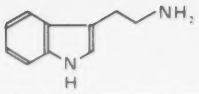
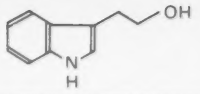
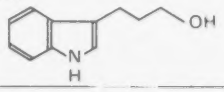
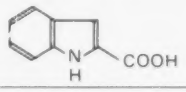
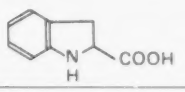
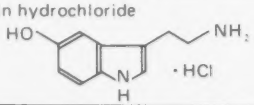
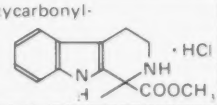
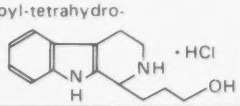
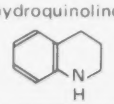
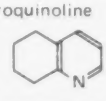
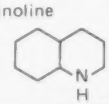
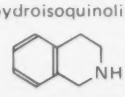
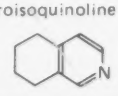
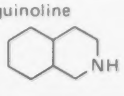
Indoline	Tryptamine 	Tryptophol 
Homotryptophol 	Indole-2-carboxylic acid 	Indoline-2-carboxylic acid 
Serotonin hydrochloride 	l-Methyl-l-metoxycarbonyl-tetrahydro-β-carboline hydrochloride 	l-Hydroxypropyl-tetrahydro-β-carboline hydrochloride 
1,2,3,4-Tetrahydroquinoline 	5,6,7,8-Tetrahydroquinoline 	Decahydroquinoline 
1,2,3,4-Tetrahydroisoquinoline 	5,6,7,8-Tetrahydroisoquinoline 	Decahydroisoquinoline 

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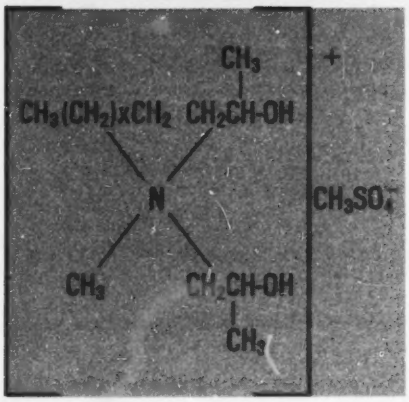

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ingredients in Robins' prescription drugs, Lee makes doxapram, guaifenesin, methocarbamol, metoclopramide, phenylephrine, and polycarbophil calcium. The weight-loss drug fenfluramine may be custom-synthesized outside. The rest are generics that the company buys.

A custom synthesis firm that lands Robins' business to make a newly discovered drug has a good chance of staying with the firm through commercial production. As Robins' Welstead explains, "We always go to Lee first with a commercial drug. Sometimes they can produce it for us. More often, they can't." But a custom synthesis firm has to be nimble to deal with Robins. "We have to be fast and flexible," Welstead says. "That's how we can compete with the giants."

Things go a little differently at medium-sized drug companies such as McNeil. The firm has a pilot plant and, as a subsidiary of Johnson & Johnson, has access to some commercial production resources within that company. Thus by the time a custom synthesis firm is called in to bid on a McNeil drug or advanced intermediate, Vasken Paragamian already has developed the process in the pilot plant, and approval is estimated to be only two to three years away. This means that the risk of staying through perhaps 10 lean years of development with the ever-present possibility of sudden death is absent. But the outside firm is now trying to come in as low bidder and one of two qualified suppliers.

There are opportunities, however, for custom synthesis firms to do dangerous reactions for McNeil even in development years. Because the pilot plant is in a residential community, Paragamian will not consider high-pressure hydrogenation, nitration, phosgenation, or use of cyanide salts there.

At large companies such as Parke-Davis, almost the only opportunities for custom suppliers are tolling of intermediates through one hazardous step during development years or production of anticancer drugs. (Tolling is use of raw materials supplied by a customer to produce a product for the customer.) Even in the field of cytotoxic anti-

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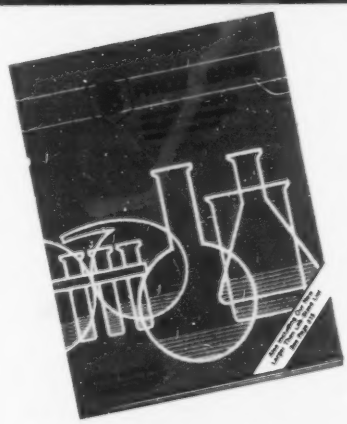

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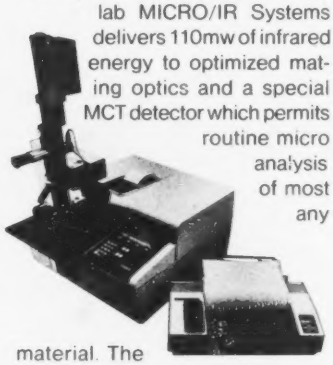

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cancer drugs, the company already has installed facilities to test small amounts of such substances safely. Marketing manager Controulis says it is rare for the company's kilo lab or pilot plant to be backed up with work. Drug development occurs on such a long time scale, he says, that there is plenty of time to consider pilot plant expansions and prepare for commercial-scale production. And when it comes time to add dedicated units to the full-scale plant, Parke-Davis would do even potentially hazardous reactions in-house.

Dille indicates the situation is similar at Eli Lilly. That company has been more flexible in the past about ordering synthesis of advanced intermediates outside. But now the tendency is to make even the intermediates in-house, as far back as possible. "But how far back can you integrate?" Dille asks. "So we always find ourselves purchasing some unique intermediate."

One possibility is that the research group may invent new chemistry that doesn't fit in with Lilly's production capability. Or production may involve an established branch of chemistry that Lilly hasn't mastered. For example, Dille says the company's research turns up increasing numbers of fluorine compounds, and Lilly doesn't have chemists with expertise in or equipment that can handle fluorine chemistry. However, he says the company is considering adding these. "But we do not farm out anything at all because of safety or environmental reasons."

In addition to making drugs by organic synthesis, Lilly also produces antibiotics by fermentation. "We never farm out fermentation," Dille declares. "We have done it rarely in the past when we were out of capacity, but that won't happen in the future. . . . We ourselves would be on the lookout for custom fermentation business."

One characteristic shared by almost all custom synthesis firms is that they have other businesses to fall back on. Most often, custom synthesis grows out of the other business, as was the case of the photographic chemicals and laboratory reagents of Kodak. Or companies in custom synthesis develop the other

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The 12th Biennial Polymer Symposium is designed to bring together scientists from countries around the Pacific Basin and will include among the speakers leading polymer scientists from the USA, Japan, Australia and Hong Kong. Poster sessions are being planned to encourage participation on the part of attendees. Although topics relevant to the theme of High Performance Polymers are desirable, submissions on general polymer topics will be considered. Those interested in presenting a Poster Talk should contact Prof. Frank Harris at (216) 375-7511, University of Akron, Institute of Polymer Science, Akron, Ohio 44325. Fees include 3 nights at the Intercontinental with breakfast and dinner, and the symposium registration fee, as well as airport transfers, lei greeting, coffee breaks, flight bag and applicable services and tax.

WEDNESDAY EVENING, December 12, 1984—Registration & Welcoming Reception

THURSDAY MORNING, December 13, 1984—*Ordered Polymers*: J. Economy, General Chairman (Opening Remarks); G. Berry, Presiding (Introduction and Overview); P. J. Flory, Stanford University, "Thermotropic Liquid Crystalline Materials"; C. L. Choy, The Chinese University of Hong Kong, "Thermal Conductivity and Expansion of Oriented Polymers"; D. G. Baird, Virginia Polytechnic Institute, "Structure & Morphology Development in Thermotropic Systems"; G. Berry, Panel Discussion.

THURSDAY EVENING, December 13, 1984—*Polymers as Ceramic Precursors*: K. Wynne, Presiding (Introduction and Overview); R. West, University of Wisconsin, "Polysilane High Polymers and Their Technological Applications"; K. Okamura, Tohoku University, "Polycarbosilanes: Preceramic Polymers"; K. Wynne, Panel Discussion.

FRIDAY MORNING, December 14, 1984—*Advanced Matrix Materials*: N. Johnson, Presiding (Introduction and Overview); E. J. Kramer, Cornell University, "Network Effects on Deformation of Glassy Polymers"; R. L. vanDeusen, Wright-Patterson Air Force Base, "Synthesis & Characterization of Higher Performance Structural Materials"; A. F. Yee, General Electric Company, "Micro Macroscopic Approaches to Tough Plastics"; N. Johnson, Panel Discussion.

FRIDAY EVENING, December 14, 1984—*Polymer Division Award Address*: G. L. Donaruma, Presiding; W. Stockmayer, Dartmouth, "Perspective on Contributions of John D. Ferry to Polymer Science"; J. D. Ferry, University of Wisconsin, "Fibrinogen—A Megabiomonomer; Fibrin—A Hyperbiopolymer"; Polymer Division Award Reception and Dinner.

SATURDAY MORNING, December 15, 1984—*Radiation Sensitive Polymers*: M. J. Bowden, Presiding, (Introduction and Overview); J. H. O'Donnell, University of Queensland, "Mechanism of Degradation of Radiation Sensitive Polymers"; C. G. Willson, IBM Research Laboratory, "Chemical Amplification in Polymeric Imaging Systems"; M. Hasegawa, University of Tokyo, "Topochemical Synthesis and Photochemical Behavior of Radiation Sensitive Polymers"; M. J. Bowden, Panel Discussion.

business, like the line of generic drugs Orsynex plans to produce.

Kodak's St. George says the company got into custom synthesis as a result of continuous inquiries from drug company researchers for 5 to 100 kg of compounds they previously had bought in small amounts through the catalog. "We see custom synthesis as a natural tie-in with photographic chemicals," says St. George. "We've developed the skills to go from the laboratory to commercial scale," he adds, pointing to the wide variety of chemical reaction types used to make photographic chemicals.

One weakness in custom synthesis at Kodak, however, is that the company limits the types of reactions it will carry out. It does some phosgenations and Grignard reactions, but it will not do high-pressure hydrogenations, polynitrations, or lithium aluminum hydride or Birch reductions, for example.

Another company that grew into custom synthesis from another business is Hardwicke Chemical Co., Elgin, S.C., a subsidiary of Ethyl Corp. since 1978. President James Hardwicke founded the company in 1967 to make intermediates for synthetic pyrethroid insecticides. A Hardwicke specialty today is bromination, but it does no other dangerous reactions. Hardwicke says that most of the company's equipment is geared to liquid chemicals, but he will install more solids-handling units as the company expands more toward servicing the drug industry.

Houle of Orsynex intended from the beginning to offer a combination of unusual and dangerous reactions. The only dangerous reaction Orsynex will not take on is nitration. Its Essex parent made a couple of false starts entering the custom synthesis business. It first acquired Minerec Corp., Baltimore, in 1979, which makes phosgene among its products. But the plant there could not be upgraded to the desired level. In 1981, Essex began operating the South Haven, Mich., plant of Wyckoff Chemical Co., but ended that arrangement, too. Acquisition of the Columbus plant finally set the company on the road to its goal. □